Draft Guidance for Industry and FDA Staff

Saline, Silicone Gel, and Alternative Breast Implants

DRAFT GUIDANCE

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For questions regarding this document contact Ms. Samie Allen at 301-519-370, ext.139 or by email at sxn@cdrh.fda.gov.

When final, this document will supersede "Guidance for Saline, Silicone Gel, and Alternative Breast Implants" dated February 11, 2003.

C·D·R·H
Center for Devices and Radiological Health

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Plastic and Reconstructive Surgery Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation

Preface

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Draft Guidance for Industry and FDA Staff

Saline, Silicone Gel, and Alternative Breast Implants

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance document, when final, will identify device description, preclinical, clinical, and labeling information that we recommend be presented in a premarket approval (PMA) application. This guidance document may also be useful in the preparation of a product development protocol (PDP), an application for an investigational device exemption (IDE), a reclassification petition, or a master access file (MAF). The information discussed pertains to breast implants filled with saline, silicone gel, or alternative filler intended for breast augmentation, breast reconstruction, and/or revision. This guidance document does not address tissue expanders, which are reviewed under the premarket notification (510(k)) process.

This version of the guidance document updates the information described in "Guidance for Saline, Silicone Gel, and Alternative Breast Implants" dated February 11, 2003. The 2003 version of this guidance document has proved useful to both sponsors and FDA in preparing and reviewing PMAs for saline-filled breast implants. FDA, sponsors, and the clinical community have learned a great deal about silicone gel-filled breast implants over the last 10 years. Accordingly, this version of the guidance document reflects the latest thinking in science and medicine pertaining to breast implants. The primary changes are to the ***Mechanical Testing***, ***Modes and Causes of Rupture*** (which replaces the previous Retrieval Study section), ***Clinical Studies***, and ***Labeling*** sections.

This guidance document supplements other FDA publications on PMA, PDP, and IDE applications and should not be construed as a replacement for these documents. For general information about these applications, see CDRH's Device Advice website as follows: PMAs (21 CFR Part 814), http://www.fda.gov/cdrh/devadvice/pma/; PDPs (21 CFR § 814.19), http://www.fda.gov/cdrh/devadvice/pma/app_methods.html; and IDEs (21 CFR Part 812), http://www.fda.gov/cdrh/devadvice/ide/index.shtml. Sponsors are responsible for developing clinical protocols and providing reasonable assurance of the safety and effectiveness of their devices.

FDA's guidance documents, including this guidance document, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

2. Background

There are three types of breast implants, all of which may be intended for breast augmentation, breast reconstruction, and revision.

2.1 Saline-Filled Breast Implant

A saline-filled breast implant has a silicone rubber shell made of polysiloxane(s), such as polydimethylsiloxane and polydiphenylsiloxane, which is inflated to the desired size with sterile isotonic saline. Saline-filled breast implants may vary in shell surface, shape, profile, volume, and shell thickness. Most have valves that self-seal and a patch that covers the manufacturing port. The sterile saline used as a filler material should conform to United States Pharmacopeia (USP) standards for Normal Physiological Saline (injection grade), which has a concentration of 0.15M and a pH of 7.2-7.4.

There are three types of saline-filled breast implants. One type is a fixed volume implant with a single lumen that is intraoperatively filled with the entire volume of saline via a valve. A second type is an adjustable volume implant with a single lumen that is intraoperatively filled with saline via a valve and has the potential for further postoperative adjustment of the saline. A third type is a prefilled saline implant.

In the Federal Register of June 24, 1988 (53 FR 23856), FDA issued a final rule classifying the silicone inflatable (saline-filled) breast prosthesis into Class III (21 CFR § 878.3530). On January 6, 1989 (54 FR 550), FDA published a notice of intent to require submission of PMAs for these devices. On January 8, 1993 (58 FR 3436), FDA issued a proposed rule to require submission of PMAs or completion of PDPs. On August 19, 1999 (64 FR 45155), FDA issued a final rule requiring PMAs for these devices to be filed with FDA, or PDPs to be completed, within 90 days. Thus, an approved PMA or PDP is now required to market a saline-filled breast implant.

2.2 Silicone Gel-Filled Breast Implant

A silicone gel-filled breast implant has a silicone rubber shell made of polysiloxane(s), such as polydimethylsiloxane and polydiphenylsiloxane, which is filled with a fixed amount of silicone gel. Silicone gel-filled breast implants may vary in shell surface, shape, profile, volume, and shell thickness. Most have a patch that covers the manufacturing port.

There are three types of silicone gel-filled breast implants. One type is a fixed volume implant with a single lumen containing a fixed amount of silicone gel. A second type is an inflatable double lumen implant with the inner lumen containing a fixed amount of silicone gel and the outer lumen

designed with a valve for filling with saline intraoperatively. A third type is an inflatable double lumen implant with the outer lumen containing a fixed amount of silicone gel and the inner lumen designed with a valve for filling with saline intraoperatively, with the potential for postoperative adjustment.

In the Federal Register of June 24, 1988 (53 FR 23856), FDA issued a final rule classifying the silicone gel-filled breast prosthesis into class III (21 CFR § 878.3540). On January 6, 1989 (54 FR 550), FDA published a notice of intent to require submission of PMAs for these devices. On May 17, 1990 (55 FR 20568), FDA issued a proposed rule to require submission of PMAs or completion of PDPs. On April 10, 1991 (56 FR 14620), FDA issued a final rule requiring PMAs for these devices to be filed with FDA, or PDPs to be completed, within 90 days. Thus, an approved PMA or PDP is now required to market a silicone gel-filled breast implant.

2.3 Alternative Breast Implant

An alternative breast implant typically has a silicone rubber shell with a filler other than saline or silicone gel. The filler material may or may not be a gel. However, an alternative breast implant may also have an alternative shell other than one made from silicone rubber. We may recommend alternative or additional evaluations of alternative breast implants depending on their design, materials, and performance characteristics.

All alternative breast implants are class III post-amendment devices that require an approved PMA or PDP for marketing. (Federal Food, Drug, and Cosmetic Act (FDCA) §§ 513(f) & 515(a) (21 U.S.C. §§ 360c(f) & 360e(a)).)

3. Device Description

The ***Background*** section above (Section 2) provides a very basic device description for each of the three types of breast implants. This section recommends the type of device description information you should include in your application. However, depending on the particular design of your device, additional information may be appropriate.

We recommend that you provide the following device description information (if applicable):

- a written description of each component that comprises the device (e.g., shell, gel, patch, textured surface, valve)
- the specific materials (with suppliers) for each component
- a description of any connector systems, fill tubes, and injection domes, including materials
- a magnified sketch of each style of device, depicting the placement/use of the connector systems, fill tubes, and injection domes
- a description of when the device is filled by the surgeon if not a prefilled device (i.e., intraoperatively and/or postoperatively)
- a description of any overexpansion/overfill of the filler material, even if on a temporary basis

?? a description of the method by which the device is sterilized

?? a summary table of all devices under review in the submission (see example table below):

Style	Shell Surface	Shape, Profile	Volume (cc)	Width (cm)	Height (cm)	Projection (cm)	Shell Thickness (mm)
XXXX	Smooth	Round, High	125-650	9-16	8.4-15	3.1-5.7	0.015”-0.040”

Depending on the specific design features of your device, we may recommend that you include additional information in your summary table. For example, if there is overexpansion of your device or your device has a combination saline/silicone gel design, you should include a column to capture pertinent information.

4. Chemistry

4.1 General Information

We recommend that you provide the following general information regarding the chemicals/materials used in the manufacture of your breast implant:

?? the common names and trade names of each chemical/material (including additives, plasticizers, and antioxidants)

?? the specific role of each chemical/material in the manufacturing process and/or in the final device

?? the location of the material within the device (e.g., shell, filler, valve, adhesive)

?? the chemical name, the mean molecular weight, and a measure of the polydispersity for each polymeric component

?? material safety data sheets for each chemical

?? MAF numbers for each material, including specific volume and page number references.

We also recommend that you state whether the silica used in the elastomer shell dispersion is in the amorphous form or the crystalline form.

Sections 4.2 through 4.5 of this document describe chemical analyses of the elastomer shell (including the patch and valve) that we recommend you describe in your submission. Sections 4.6 through 4.9 describe chemical analyses of the filler material. Additional analyses may be appropriate due to changes in design features, such as texturing, variations of device components, such as patches or valves, or changes in sterilization.

4.2 Extent of Crosslinking

The manufacture of the shell involves curing of polymeric components of silicones by chemical crosslinking. We recommend that you provide the extent of crosslinking from at least three different lots to confirm the uniformity of the degree of crosslinking across lots. Suggested methods to determine the extent of crosslinking include:

- ?? measurement of Young's modulus at low strain (this is approximately proportional to crosslink density)
- ?? measurement of equilibrium swelling of the polymeric component by a good solvent
- ?? determination of the amount of unreacted crosslinker from the total extractables
- ?? any other acceptable scientific method.

We recommend that you also perform a Fourier Transform Infrared Spectroscopy (FTIR) analysis on the cured polymer to confirm the presence of silicone functional groups.

4.3 Extractables

We recommend that you conduct an analysis of the extractable or releasable chemicals to identify potentially toxic chemicals and estimate the upper limits of the chemicals that could be released into the patient. Although other methods may be used, the following is one suggested method for obtaining extractable data:

> Perform the extraction of the shell for chemical analyses with at least one polar solvent (i.e., ethanol or a mixture of ethanol-water) and two non-polar solvents (i.e., dichloromethane and hexane) at 37?C. To determine the duration of the exhaustive extractions, you should conduct a series of successive extractions by exposing the sample to the solvent for a period of time, analyzing the solvent for extractables, replacing with fresh solvent, exposing the sample again for a period of time, analyzing, and repeating the process.
> When the level of the analyte for the extraction is one-tenth (0.1) the level in the previous extraction, the extraction is deemed complete so that a 10% correction to the total extractable material can be applied. In cases where this condition may not occur because of extremely slow migration of the higher molecular weight material, you should apply the test to the contents of the extract with molecular weights of ?1500 Daltons because these are the compounds of greatest interest. You should add all separate analyte levels to calculate the cumulative value and, via the sample/solvent ratio, the sample and device levels. You should use the total extraction from the polar solvent and the extraction from one of the non-polar solvents that yields the higher amounts of extractables for both quantitative and qualitative analyses. For extracts that may contain oligomeric or polymeric species, you should provide the molecular weight distribution, along with the number and weight average molecular weights and the polydispersity. You should perform an FTIR analysis on the extractable residuals.

We recommend that you provide the following information from your analyses of the extractables:

- ?? identification and quantification of all compounds below a molecular weight of ?1500

Daltons after exhaustive extraction of the final sterilized shell. These should include, but need not be limited to:

- residual monomers, cyclic and linear oligo-siloxanes
- known toxic residues such as polychlorinated biphenyls (PCBs), if peroxide curing process is involved
- aromatic amines, if polyurethanes are used

?? the percent recovery, especially for the polydimethylsiloxanes (up to D20)

?? evidence that shows that exhaustive extraction has been achieved with one of the solvents

?? identification of all experimental methodology[1]

?? raw data (including instrument reports) with all chromatograms, spectrograms, etc. You should also provide the practical quantitative limit when the analyte of interest is not detected.[2]

4.4 Volatiles

We recommend that you analyze the elastomer shell for volatile components using a headspace detector.

4.5 Heavy Metals

We recommend that you provide qualitative and quantitative analyses for heavy metals on the final finished shell. The heavy metal analyses should include, but need not be limited to, analyses of the following metals: platinum (Pt); tin (Sn); zinc (Zn); chromium (Cr); arsenic (As); lead (Pb); antimony (Sb); nickel (Ni); and copper (Cu). In addition, for the metal used as the catalyst in the curing reaction, we recommend that you provide the valence state and the amount of residue of the catalyst.

In lieu of providing a complete heavy metal analysis on the finished shell, you may provide the purity of the catalyst (with trace elements) used in the raw shell material, along with an analysis of the finished shell for just the catalyst metal used.

4.6 Saline Filler

Normal physiological sterile saline has a long history of use in breast implants and is standardized by the USP. As stated above, the sterile saline used with your device should conform to USP standards for Normal Physiological Saline (injection grade), which has a concentration of 0.15M and a pH of 7.2-7.4. If your breast implant is used with any other saline, we recommend that you provide a complete chemical analysis of that saline.

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[1] For example: Gel Permeable Chromatography (GPC), Gas Liquid Chromatography (GLC), Mass Spectometry (MS), Atomic Emission Detector (AED), and FTIR.

[2] Keith, L. Compilation of EPA's Sampling and Analysis Methods. Lewis Publishers, 1992.

4.7 Silicone Gel Filler

The analyses of the silicone gel should be very similar to those for the elastomer shell. We recommend that you provide the following information on the final sterilized gel:

?? qualitative and quantitative analyses for extractables (such as cyclic polysiloxanes), including:

- characterization of the polymers present
- molecular weight averages and polydispersities of the polymers
- identification and quantification of all compounds present with a molecular weight of ?1500 Daltons

?? qualitative and quantitative analyses for volatiles

?? qualitative and quantitative analyses for heavy metal contents

?? all physical properties of the gel, including viscosity, cohesivity, and approximate crosslink density (if possible)

?? the percentage of silicone oil and its chemical and physical properties (e.g., molecular weight, viscosity).

4.8 Alternative Filler - Polymer

We recommend that you provide the following information on a final sterilized polymer filler:

- ?? the rationale for the use of the specific alternative filler material
- ?? a list of all the components used in the synthesis and the method of synthesis of any polymer used in the preparation of filler (if it is a synthetic polymer) or the source and isolation procedure of the polymer, if it is a natural polymer
- ?? quantitative analyses of monomers (if synthetic polymer) and their safety profiles
- ?? the method of purification of the polymer
- ?? complete physical and chemical characteristics of the polymer (e.g., viscosity, molecular weight)
- ?? the formulation of the polymer (the ratio of polymer should be specified if the filler material is a mixture of more than one component)
- ?? the structural analyses of the polymer, including molecular weight distribution
- ?? quantification and identification of all chemicals below a molecular weight of 1500 Daltons and their characterization
- ?? the trace metal/heavy metal analysis and the valence state if metals were used as catalysts in the polymerization reaction
- ?? the crosslink density (if it is a synthetic and cured material).

4.9 Alternative Filler – Non-Polymer

We recommend that you provide the following information on a final sterilized non-polymer filler:

- ?? the rationale for the use of the specific alternative filler material
- ?? composition of the non-polymer, including characterization of smaller molecular weight components
- ?? the method of purification of the non-polymer
- ?? complete physical and chemical characteristics of the non-polymer (e.g., viscosity, molecular weight)
- ?? the source and isolation procedure of the non-polymer
- ?? the structural analyses of the non-polymer, including molecular weight distribution.

5. Toxicology

5.1 General Information

A toxicological assessment should be conducted because breast implants contain not only the major polymeric materials (e.g., polymerized polydimethylsiloxane), but also low molecular weight components, such as monomers, oligomers, catalysts, and residues from the manufacturing or sterilization processes that may leach out into the patient's body. The toxicological safety

assessment should be based on information from:

- the chemical composition of the device (Section 4.1 above)
- pharmacokinetic studies
- the standard battery of toxicological tests.

The portion of your submission dealing with chemical composition should provide a list of the chemicals present (Section 4.1 above). Pharmacokinetic studies determine the rates of absorption, distribution, metabolism, and elimination of the substances absorbed into the patient's body (Section 5.2). The standard toxicological testing battery is used to detect unidentified toxins and to quantify the exposure to known toxic compounds (Section 5.3).

5.2 Pharmacokinetic Studies

Knowledge of the pharmacokinetic behavior of potentially toxic chemicals provides a scientific assessment of the potential of the chemicals to accumulate in the body at concentrations that cause human health risks. The pharmacokinetic study design you choose should be based on the information needed to address the worst case assumption (i.e., that all of the material in the device is absorbed into the body at once). If this assumption, with the addition of safety factors, results in toxic levels of exposure, demonstrations of slow diffusion of substances from the device into the body or rapid metabolism or excretion of the substances by the patient may negate the worst case assumption. The pharmacokinetic testing of toxins of concern should determine the rates of absorption into and clearance from the blood, the distribution in the body, and the rates of metabolism and/or excretion. If radiolabeling is used, the device should be labeled in ways that will reflect the fates of all of the components of interest. For additional information, see International Organization for Standardization (ISO) standard 10993-16.

5.3 Toxicological Testing

We recommend that you perform the standard battery of toxicological tests separately on both the final sterilized shell and filler. These tests include:

- cytotoxicity
- short and intermediate-term implantation tests
- acute systemic toxicity
- hemocompatibility
- immunotoxicity
- reproductive toxicity
- teratogenicity
- genotoxicity
- carcinogenicity (including subchronic and chronic toxicity testing).

Refer to ISO-10993, "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing," and the CDRH guidance document, "**Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'**," available at http://www.fda.gov/cdrh/g951.html, for more details about the toxicological tests above.

Refer to Section 5.4 below for special considerations regarding some of the toxicological tests.

5.4 Special Considerations

We recommend that you assess the level of immunotoxicity of the shell and any leachable compounds from the shell and the gel (if applicable). For more information, you should refer to the CDRH "**Immunotoxicity Testing Guidance,**" available at http://www.fda.gov/cdrh/ost/ostggp/immunotox.pdf.

Reproductive and teratogenicity studies should measure the rates of conception, as well as the number of fetal deaths and malformations. The studies should include at least two generations. You should test individual compounds at the highest possible exposure that does not produce non-reproductive systemic toxicity.

Genotoxicity testing addresses the potential of leachable compounds and/or degradation products of your device to cause cancer. FDA believes that genotoxicity testing may be sufficient in lieu of 2-year carcinogenicity testing if all of the short-term genotoxicity tests are negative. The short-term genotoxicity testing should consist of, but need not be limited to:

- a bacterial mutagenicity test (including point mutations and frameshift mutations)
- a mammalian forward mutation assay (e.g., a mouse lymphoma test)
- an in-vivo rodent micronucleus test.

However, even if the short-term genotoxicity testing is negative, FDA may recommend 2-year carcinogenicity testing if (1) your device consists of other materials than those typically present in polydimethylsiloxane-based breast implants or (2) your device consists of material compounds (e.g., D_4) at higher-than-expected levels.

You may combine the carcinogenicity study with the subchronic and chronic toxicity testing by removing animals from the carcinogenicity study at appropriate intervals. In this case, the carcinogenicity study should be initiated with additional animals to compensate for the animals scheduled to be removed. If, however, a subchronic or chronic toxicity emerges during the study, this may interfere with the ongoing carcinogenicity study.

We recommend that you provide subchronic and chronic toxicity testing because the leaching process may be slow, even when the material is in pulverized form, exposing the animals or cells to very small quantities of potential leachable toxicants or carcinogens. Implanted material may also degrade over time, producing toxic degradation products. These toxins might be detected only by subchronic or chronic implantation tests. The subchronic implantation test reports should include

gross and histopathology examinations of the tissue surrounding the implanted material and at appropriate sites remote from the implantation site with gross lesions or potential connections to the observed toxicity.

If the short-term genetic toxicology testing is negative and the clinical carcinogenic experience with the materials continues to support safety, you may consider completing the carcinogenicity testing concurrently with your ongoing Core Study.

6. Mechanical Testing

6.1 General Information

In general, we recommend that you design mechanical testing to be predictive of clinical modes and causes of failure during the expected life of your device. For example, whenever possible and applicable, the test methodologies should mimic in-vivo conditions (e.g., incubate the breast implants in a lipid-rich medium prior to testing and conduct testing in a physiologic environment).

We suggest that you perform individual component and total device testing to evaluate the mechanical properties of your breast implant. These tests are described in Sections 6.2-6.6 below.

We recommend that you perform all testing on finished, sterilized total devices or components (e.g., shell, gel, valve). If your device is sterilized by different methods (e.g., ethylene oxide, gamma radiation), we request that you perform the testing on samples sterilized by the different methods, or provide an adequate rationale why the change in sterilization method does not negatively impact the mechanical characteristics.

We also request that you provide complete reports for all testing, including identification of the devices tested and a description of the test set-up and methods, including sketches or photographs.

With regard to material properties, such as tensile strength, ultimate elongation, joint testing, and tear resistance, FDA believes that these can be adequately addressed through your validation and verification manufacturing activities.

6.2 Fatigue Rupture Testing of Total Device

Most materials have a finite fatigue life when repeatedly stressed in-vivo. Repeated stressing of the device may eventually weaken the shell and lead to failure.

When designing your fatigue testing protocol, FDA recommends that you carefully consider the test methodology, such as the loading direction(s) on the device, the shape of the loading apparatus that contacts the devices, the testing medium, etc. We have found that the current test methodology, in which flat plates compress the device in air, is not predictive of clinical failure. More specifically, results of testing using this method show that breast implants should not rupture even at loads much greater than those expected in-vivo. However, because current clinical information indicates that devices do rupture, even at early timepoints, the validity of this test methodology is questionable. A

test methodology that replicates clinical failure mode(s) should approximate the rate of rupture during the expected life of your device. FDA believes that retrieval study data, which accurately define the mode(s) and cause(s) of rupture, may be helpful in the design of the new test methodology.

Therefore, we recommend that you provide a complete test report of fatigue testing on the worst case, final, sterilized device(s) with the thinnest shells allowed by the design release criteria using a test set-up with particular focus on the loading direction(s) on the device, the shape of the loading apparatus that contacts the device, the testing medium, etc., that mimics expected in-vivo loading.

Fatigue testing should be performed in a constant load or a constant displacement mode. However, you should perform constant displacement testing only if you measure the actual applied loads continuously or at frequent points during the testing and the variation of the actual applied load is minimal. You should use the minimal load applied during constant displacement testing to establish the endurance load level.

You should cyclically load the samples to runout or failure at varying loads or displacements to generate an applied force versus number of cycles (AF/N) curve for the worst case device(s). You should base the runout value on the expected in-vivo cycles that the device will be subjected to in its lifetime, and you should provide an adequate rationale for the runout value.

You should test a minimum of 3 samples at a given load or displacement from static point down to the endurance load level because of the general variance seen in elastomer testing. You should start with the static point and keep reducing the load or displacement for each subsequent test until a sample can reach runout without failure. Whether load or displacement control testing is performed, you should provide an AF/N curve for each style of device tested. These curves may be generated by best-fit approach or by averaging the number of samples tested to establish a given point. There should be a tight range (e.g., 10%) of points around and at the endurance load level for a cleaner curve.

We recommend that you provide the following results for each style of device tested:

- the resulting endurance load level
- the clinical relevance for the resulting endurance load level, including the incorporation of a safety factor
- the AF/N curve
- the raw data
  - applied loads
  - applied displacements (only for displacement control test)
  - corresponding number of cycles to failure (unless runout reached)
  - sample thicknesses.

6.3 Valve Competency Testing

This testing pertains only to breast implants with valves. Valve competence tests are performed to demonstrate that valve integrity is maintained at in-vivo loads. Devices can be subjected to hydrostatic forces that tend to force fluid out of the device, causing a deflation and change in size and shape. The most likely source for increased pressure inside the devices would be from patients reclining with various body parts (e.g., head, arm, trunk) pressing on their devices.

ASTM standard F2051 states that there shall be no leakage observable after a normally closed valve is subjected to a retrograde pressure equivalent to 30cm H_2O for 5 minutes and then to a retrograde pressure equivalent to 3cm H_2O for 5 minutes. FDA does not believe that the ASTM F2051 methodology is clinically relevant with respect to the load levels. However, this methodology may provide useful information about the valve handling shifts in pressure. Therefore, you should provide a complete report of valve competency testing as per ASTM F2051. You should also provide the pass/fail results for leakage.

In addition to the testing above, you should provide a complete report of destructive testing to address in-vivo loading conditions. You should gradually load the samples until valve failure occurs to define a maximum pressure for the device. We recommend that you provide the following results:

- the burst pressures
- the failure modes (including whether the failed test valves reseal upon removal of the excess failure-inducing pressures)
- the rationale why the resulting burst pressures are clinically relevant.

6.4 Cohesivity Testing

This testing pertains only to silicone gel-filled and alternative breast implants.

Cohesivity of Silicone Gel-Filled Breast Implants

We recommend that you quantify the cohesivity of the silicone gel. Although the two methods described in ASTM F703 were not developed to address gels with high cohesivities, the results provide useful device characterization information. We recommend that you provide the complete reports of the following testing to address gel cohesivity:

- gel cohesion testing on the final device as described in the cone/pendant method in ASTM F703
- penetration testing (an indirect measure of gel cohesivity) on the in-process gel.

For the gel cohesion testing, we recommend that you provide the pass/fail results.

For the penetration testing, we recommend that you provide a complete description of the penetration test method, the acceptance criteria, and the results.

Cohesivity of Alternative Breast Implants

Depending on the filler of your alternative breast implant, FDA may recommend that you provide cohesivity testing similar to that described above for silicone gel-filled breast implants.

6.5 Bleed Testing

This testing pertains only to silicone gel-filled and alternative breast implants.

Bleed of Silicone Gel-Filled Breast Implants

Silicone gel bleed is the diffusion of gel constituents (e.g., low molecular weight silicones) through an intact shell. Although current designs of breast implants should minimize gel bleed, gel bleed appears to occur continuously for silicone gel-filled breast implants.

The ASTM F703 test methodology quantifies the extent of gel bleed. However, the results from this testing would have limited clinical correlation because the ASTM F703 test method was established for the purpose of allowing comparison between device models rather than quantifying in-vivo gel bleed. In addition, the ASTM F703 test method was not established to identify and quantify the gel bleed constituents. Thus, FDA does not believe that this test methodology provides adequate data to address gel bleed for the purposes of a PMA.

Accordingly, we recommend that you provide a complete report of gel bleed bench testing based on a protocol that mimics in-vivo conditions (e.g., incubate the breast devices in a lipid-rich medium prior to testing and conduct testing in a physiologic environment). We recommend that you identity the gel bleed constituents (including the platinum species (or other catalysts)), the rate that these gel constituents bleed out, and how that rate changes over time.

Bleed of Alternative Breast Implants

For devices with alternative fillers, FDA is interested in potential changes in composition of the alternative filler resulting from long-term chronic bleed, for which there is little known information. Therefore, we recommend that, in addition to performing the testing described above for a silicone gel-filled breast implant, you provide the results of a chemical analysis of the material remaining in the device.

6.6 Stability Testing of Alternative Breast Implants

For a breast implant with an alternative polymer or non-polymer filler, we recommend that you provide a complete report of long-term stability and accelerated aging testing to demonstrate the effects of time and temperature on the physical properties and chemical composition of the device as a whole and of the filler material. You should measure key physical parameters of the filler, such as viscosity and cohesivity, at each timepoint. If there are mechanical changes, you should conduct complete chemical analyses to explain the physical changes.

7. Modes and Causes of Rupture

The modes and causes of rupture should be characterized so that both the rate of rupture and the rate of change of rupture over time can be minimized to establish reasonable assurance of device safety.

Therefore, we recommend that you provide the following to characterize the modes and causes of clinical rupture of your device:

- a retrieval study of your explanted devices (see ***Retrieval Study*** section below for more details)
- an assessment of your manufacturing processes related to release specifications of your shell to determine whether any allowances for imperfections, such as bubbles and contaminants, may be related to device rupture
- an assessment of the surgical techniques that increase the risk of rupture.

In addition, we recommend that you provide a comprehensive literature review of durability studies based on explanted devices.

This information should aid in the design of preclinical tests that predict the long-term rupture rate, encourage the design of improved devices, and establish new tests for manufacturing acceptance criteria for components or processes that contribute to device failure.

Retrieval Study

A retrieval study is intended to collect and to evaluate explanted devices. We recommend that you design your retrieval study to ensure that you will be able to successfully assess the modes and causes of rupture. The literature reports numerous factors to consider when evaluating the modes and causes of failure. Some of these factors are directly related to the breast implant or its use, while others are not. We recommend that you address the factors listed below in the design of your retrieval study. The factors should include, but need not be limited to:

- device type/model
- device size
- device shell thickness
- device surface (smooth versus textured)
- device lot (lot-to-lot variability in initial gel and shell crosslinking and mechanical properties)
- length of implantation
- device handling prior to insertion
- device position
- implantation technique (scalpel nicks, suture punctures, surgeon's finger imprints, clamp grip marks)
- in-vivo material property and chemistry changes/degradation

- in-vivo cyclic stress
- in-vivo trauma (accident, mammography)
- procedures performed while device is in-situ (biopsies, cyst aspirations)
- explantation technique.

A standard retrieval study should involve:

- data collection at the time of explantation by the surgeon or appropriate healthcare provider
- laboratory testing of the explanted devices by you or a third party.

FDA recommends the article by Brandon, et al.[3] for a description of the type of information to consider during the development of your retrieval study protocol (e.g., control group of unimplanted devices, detailed chemical analyses of materials, detailed mechanical testing, scanning electron microscopy, and analysis of local tissue/capsule).

8. Shelf Life Testing

We recommend that you provide both real-time mechanical testing and packaging testing to establish the shelf life (i.e., expiration date) for the device.

We recommend that you perform mechanical testing on representative aged samples at time zero and at various intervals throughout the claimed shelf life. The mechanical tests should include, but need not be limited to:

- ultimate elongation
- joint
- tensile set
- break force
- valve competency (if applicable)
- gel cohesivity (if applicable).

With regard to packaging testing, we recommend that you test the final finished package for initial integrity and maintenance of integrity after selecting the appropriate materials and qualifying the package configuration. You should use test methods that are either validated or standardized. Below is a more detailed description of what we recommend you provide to address initial package integrity and maintenance of package integrity.

Initial Package Integrity

[3] Brandon, et. al, "Protocol for Retrieval and Analysis of Breast Implants." Journal of Long-Term Effects of Medical Implants, 13(1): 49-61. 2003.

We recommend that you test the integrity of the seal and the whole package at time zero. This includes both seal and whole package testing. You should test the seals of the package for seal integrity and seal strength. Seal integrity may be established by demonstrating that the seal is impermeable and continuous. There are several standardized methods that may be used to determine seal integrity. For example, ASTM F1929 is a dye penetration method for detecting seal leaks. Seal strength should demonstrate that the fiber shedding, splitting, and tearing of the package is within your specifications.

For whole package testing, you may use physical or microbiological test methods. Examples of whole package integrity tests are internal pressure test, dye penetration, gas sensing test, or vacuum leak test. At the present time, there are only a few standardized physical whole package test methods. ASTM D3078 is an example of a test method by bubble emission. Alternatively, you may use a microbial challenge test.

Maintenance of Package Integrity

We recommend that you evaluate the ability of the package to maintain its integrity over time by the same functional tests used for integrity testing. You should expose the package, with the device in it, to the environmental stresses imposed by manufacturing, sterilization processes, distribution, handling, vibration, and the storage environment. You should perform the seal integrity and whole package testing after stressing and at various intervals throughout the claimed shelf life of the package. The data obtained during this time period should remain within the validated limits of the performance specification.

9. Clinical Studies

9.1 General Information

FDA requests that the Core Study (i.e., the primary IDE study used to support PMA approval) involve 10 years or more of prospective patient follow-up, including some premarket and some postmarket follow-up. The extent of premarket follow-up data (clinical and preclinical) should be sufficient to address specific safety concerns, such as the rates of complications (e.g., rupture, reoperation) and their potential health consequences, and to reasonably predict the safety profile of the device over its lifetime. Depending on the data, 2 years of premarket clinical data may not be sufficient to evaluate the safety and effectiveness of your device, whether it is a saline-filled, silicone gel-filled, or alternative breast implant. For example, because of the difficulty in detecting rupture and the risk of extracapsular and migrated silicone gel, additional years of premarket follow-up may be recommended for silicone gel-filled breast implants.

We recommend that studies include the separate patient cohorts of primary augmentation, primary reconstruction, and revision. Because these studies are complicated by the fact that some patients receive devices for different reasons (e.g., a woman may receive one device for reconstruction and one for augmentation), we also recommend that you record and analyze the data on both per patient and per device bases. We recommend that you classify the patient and device by the initial indication at study *entry* as follows:

- If a reconstruction patient undergoes contralateral augmentation, that *patient* would be classified as reconstruction. The device would be classified as one reconstruction and one augmentation.

- If a revision patient (i.e., the patient entered the study due to replacement of an existing device, regardless of the type or manufacturer of the original device), undergoes contralateral augmentation, that *patient* would be classified as a revision patient. The device would be classified as one revision and one augmentation.

- Even if a revision (removal with replacement) occurs during the study (i.e., after initial implantation), the *patient* and *device* would continue to be classified based on the original indication (i.e., primary augmentation, primary reconstruction, or revision).

If patients undergo removal and replacement with your device, FDA recommends that you continue follow-up of these patients. For patients who undergo removal without replacement, or removal with replacement with another manufacturer's device, FDA still encourages you to continue follow-up evaluations.

Refer to Section 10 for FDA's recommendations regarding the clinical data presentations that you should provide for breast implants.

9.2 Clinical Study Design/Statistical Analyses

Clinical Study Design

We recommend that you provide a complete description of your Core Study. This includes:

- study objectives
- primary and ancillary hypotheses
- definitions of the study population (i.e., inclusion and exclusion criteria)
- methods of randomization, if applicable
- number and locations of investigational sites
- enrollment procedures
- description of surgical techniques
- description of allowable ancillary surgical interventions and/or drugs
- description of chemotherapy, radiation, or other cancer treatments on all reconstruction patients and on augmentation and reconstruction patients who develop breast cancer during the course of the study (these treatments can impact the development of local complications with devices and, thus, impact the evaluation of the safety and effectiveness of the device)
- description of the control group (see paragraph below).

If you choose to incorporate a concurrent control group, we recommend that you select an approved saline-filled breast implant. If you choose not to incorporate a concurrent control group, we recommend that you use historical controls and provide the rationale for not using a concurrent control group.

Sample Size

We recommend that you provide the statistical rationale for why the sample size is adequate to evaluate the device. This should include, but need not be limited to:

- identification of effect criteria (i.e., clinically significant difference in the response variables to be detected)
- desired precision for rate estimates (i.e., defined as ½ width of confidence interval)
- statistical error tolerances of alpha and beta
- anticipated variances of response variables (if known)
- any assumptions or statistical formulas with a list of references used
- reasonable estimations of lost-to-follow-up rates
- all calculations used.

We recommend that you base sample size estimates on the precision of safety and effectiveness outcomes or the detection of a clinically meaningful difference at 2 years from baseline or from a control group, taking into account the lost-to-follow-up rates estimated for 10 years of patient follow-up. If sample size estimates are based on the precision with which complication rates can be estimated, then the sample size should be large enough to ensure that this precision is within a pre-specified number of percentage points based on 95% confidence intervals.

For example, for sufficient numbers of patients with primary augmentation or primary reconstruction (i.e., assuming 75% primary augmentation and 25% primary reconstruction) to determine the rupture rate with a precision as follows, data on 500 patients would be needed at 10 years post-implantation. If you estimate a hypothetical 40% drop out rate at 10 years, then you should enroll at least 850 patients to achieve 10-year data on 500 patients. This will provide a worst case precision of +/-4% at a rupture rate of 50%. This precision will improve as the rate moves away from 50%, with a +/-1.9% precision at a rupture rate of 5% or 95%. This pooling of cohorts represents the overall worst case precision. However, FDA recommends that you provide the precision (i.e., confidence intervals) separately for each patient cohort.

Because both safety and effectiveness data from patients presenting for revision may be significantly different from data from primary implantation patients, you should include a proportion of patients presenting for revision. For example, if you estimate that approximately 20% of patients present for breast implants due to revision, you should increase the final sample size by 20%. Therefore, if you need 850 primary implantation patients, you should enroll approximately 150 revision patients, for a total of 1000 patients.

You should support all marketing claims of equivalence or superiority to existing implants or therapies with statistically justified numbers of patients, clinically relevant endpoints, and direct comparisons made to an appropriate control group.

Lost-to-Follow-Up Analyses

Please note that high lost-to-follow-up rates may affect FDA's ability to evaluate your PMA. Therefore, we recommend that you include a comparison of baseline characteristics between those subjects with complete data and those without to ascertain the presence of any non-respondent bias. We recommend that you contact patients who are lost-to-follow-up at the end of the study to determine whether the outcomes for these patients are the same as those for the patients who were compliant with follow-up. Failure to do this may delay filing and/or approval of the PMA because additional clinical studies may be recommended.

9.3 Safety Assessment

Complications

Information about the complications below is important in determining the safety of breast implants.[4] Therefore, we recommend that you provide the following information, regardless of whether or not the complications may be related to the device:

- the incidence, timing, and reason(s) for all device removals, including removal followed by replacement with your device, removal followed by replacement with another manufacturer's device, and removal without replacement.[5] Reasons for removal may include capsular contracture, rupture/leakage, breast pain, wrinkling, change in size/shape, etc.

- the incidence, timing, and reason(s) for any reoperation (additional operation). Reasons for reoperation may include rupture/leakage, wrinkling, ptosis, asymmetry, change size/shape, etc.

- the incidence, timing, and type(s) of additional surgical procedures. Multiple types of surgical procedures may be performed in a given reoperation. Types of additional surgical procedures include capsulotomy, capsulectomy, device removal followed by replacement, device removal without replacement, saline adjustment, reposition of device, drainage of abscess/hematoma/seroma, excision of masses/lymph nodes in ipsilateral axilla or arm of implanted breast, biopsy/cyst removal, etc.

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[4]Safety of Silicone Breast Implants. Institute of Medicine National Academy Press, Washington, D.C. 2000. [IOM Report]

[5]As stated in Section 9.1, if a patient undergoes removal and replacement with your implant, then you should continue follow-up on that patient. For a patient who undergoes removal without replacement or removal followed by replacement with another manufacturer's implant, FDA still encourages you to continue follow-up evaluations on that patient.

- the incidence, timing, and resolution of all other complications, such as rupture (see appropriate rupture section below for more details for silicone gel-filled and alternative breast implants), capsular contracture (include Baker Grade), infection, calcification, migration, extrusion, skin erosion, necrosis, lymphadenopathy, delayed wound healing, breast/chest/axillary mass formation, iatrogenic injury, hematoma, pain, seroma, wrinkling, asymmetry, scar formation, visibility of the device, etc.

- the incidence, timing, and severity of alterations in nipple or breast sensation

- the incidence, timing, and severity of interference and/or difficulties with lactation

- the incidence, timing, and nature of difficulties with pregnancy

- the incidence, timing, and cause of patient deaths (the causes of death should be taken from post-mortem examinations)

- the incidence, timing, and type of new breast cancer diagnosis post-implantation, including any mammographic difficulties/interference caused by the device.

FDA recommends that you conduct regularly scheduled evaluations of these complications. We suggest follow-up frequencies of 6-10 weeks, 1 year, and annually thereafter, if not more often. We recommend that you perform annual visits to minimize the number of patients who are lost-to-follow-up.

Rupture of Silicone Gel-Filled Breast Implants

FDA believes that device rupture is one of the primary safety concerns presented by breast implants. When a silicone gel-filled breast implant ruptures, the patient and the physician may be unaware of it, the body does not have a mechanism for eliminating the silicone gel, and the gel can migrate outside of the capsule into the breast area, the lymph nodes, and distant locations (i.e., extracapsular gel migration). Accordingly, FDA recommends that you provide:

- the rate and rate of change of rupture over the expected lifetime of the device (see paragraph below)

- the frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel for all patients with ruptured devices (both symptomatic and asymptomatic (silent rupture) patients). For all patients with ruptured devices undergoing explantation, we recommend that you provide tissue sampling results from the surrounding breast tissue and capsule to confirm whether or not device constituents are present, either from the gel or from the device shell due to wear
- a detailed description of the local health consequences for all patients with ruptured devices (both symptomatic and asymptomatic (silent rupture) patients), including the severity of these health consequences and the clinical course of these patients.

To obtain complete rupture rate data (1st bullet above), we recommend that your Core Study capture silent rupture rates via prospective, sequential screening of a subgroup of the study population utilizing diagnostic radiographic or other techniques of comparable sensitivity and specificity.

For silicone gel-filled implants, FDA recommends magnetic resonance imaging (MRI) as the current method of choice for detecting silent rupture. MRI of the breast should be performed with a dedicated breast coil and preferably in centers experienced in performing and interpreting this type of examination. The MRI films should be read by both the local radiologist at the center performing the exam and by a radiologist experienced in reading breast implant MRIs (i.e., qualified MRI assessor). The radiologists should be masked to the investigator's judgment of a possible rupture (if applicable) and should each perform an independent assessment of each MRI and rate the presence or absence of rupture as definitive, suspicious/indeterminate, or none/intact.

For devices that are explanted, the final rupture determination should be made at the time of explantation. If explantation is not performed for devices reported as definitive or indeterminate for rupture via MRI, then the readings by both the qualified MRI assessor and the local radiologist should be reported. FDA recommends that the patients in the silent rupture cohort undergo MRI evaluations at 1, 2, 4, 6, 8, and 10 years, if not more frequently.

The sample size of the silent rupture cohort should be sufficient to characterize the expected rupture rate and the expected follow-up rate through the 10-year period suggested above. The duration of follow-up of the MRI cohort, as well as the follow-up rates of the MRI cohort, should adequately define the silent rupture rate and, accordingly, the overall rupture rate.

If, because of the mechanical or chemical properties of your device, rupture cannot be visualized using MRI, we recommend that you develop an alternative method with comparable sensitivity and specificity.

Rupture of Alternative Breast Implants

Depending on the filler of your alternative breast implants, FDA may recommend that you provide similar rupture information as that described above for silicone gel-filled breast implants.

Connective Tissue Diseases (CTDs)

FDA recognizes that much has been learned over the last decade on this issue, including data and analysis from the 1999 IOM Report on the Safety of Silicone Breast Implants, and that the Core Study is not designed to examine a potential linkage between breast implants and the development of CTDs. We do, however, recommend that a sponsor collect information on diagnoses of CTD as part of the overall safety assessment on its device. We recommend that you provide information on the following CTD diagnoses for patients enrolled in the Core Study:

?? rheumatic diseases – such as rheumatoid arthritis, systemic lupus erythematosus, discoid lupus, scleroderma, vasculitis, polymyositis, and dermatomyositis

?? rheumatic syndromes – such as Raynaud's phenomenon, Sjogren's syndrome, CREST syndrome, morphea, carpal tunnel syndrome, multiple sclerosis-like syndrome, multiple myeloma-like syndrome, chronic fatigue syndrome, and fibromyalgia.

In addition, we recommend that you provide information on the following CTD signs and symptoms in order to provide complete information to patients who may consider getting breast implants:

?? rheumatic signs and symptoms - such as hair loss, facial rash, photosensitivity, dry eyes, dry mouth, arthralgias, myalgias, difficulty swallowing, morning stiffness >30 minutes, ocular inflammation/retinitis/optic neuritis, muscle weakness, joint swelling for >6 weeks, pleurisy, skin rash, and lymphadenopathy

?? other reported signs/symptoms - such as cognitive dysfunction, fatigue, paresthesia, dizziness, abnormal bruising or bleeding, purpura, unexplained fever, urticaria, telangiectasia, and petechiae.

FDA recommends that you conduct CTD evaluations on all patients at the preoperative timepoint and at the 1, 2, 4, 6, 8, and 10-year postoperative timepoints. If indicated, patients should have follow-up evaluation(s) by a rheumatologist or other appropriate specialist with collection of serological information (e.g., anti-nuclear antibody (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), immunoglobulin levels, c-reactive protein (CRP), serum protein electrophoresis (SPEP), complement levels).

9.4 Effectiveness Assessment

Anatomical Effect

We recommend that you provide data on the anatomical effect of the device. This may be accomplished by comparing matched analyses of before and after bra and cup sizes, chest circumference, symmetry, and/or other standardized measurements.

Health Related Quality of Life (HRQL)

We recommend that you provide the results from HRQL assessments to assess the beneficial impact of the device. You should include these assessments as secondary endpoints of effectiveness. These assessments should include, but need not be limited to:

- a measure of self esteem (i.e., Rosenberg Self Esteem Scale)
- a measure of body image (i.e., Body Esteem Scale)
- a measure of general health related quality of life (i.e., SF-36).

FDA recommends that you conduct HRQL assessments on all patients at the preoperative timepoint and at the 1, 2, 4, 6, 8, and 10-year postoperative timepoints. For reconstruction patients, you should describe the timing of administration of these instruments (delayed or immediately following reconstruction).

Satisfaction

We also recommend that you provide data on global patient satisfaction. Your assessment should incorporate the effects of:

- the initial surgical procedure
- any adjunctive surgical and medical procedures
- any complications
- whether the expected benefits of the devices have been met
- device removal, regardless of whether the device was replaced.

For all assessments, we recommend that your case report forms include detailed reasons for any dissatisfaction.

9.5 Supplemental Clinical Information

This section pertains to only silicone gel-filled and alternative breast implants.

Silicone Gel-Filled Breast Implants

Because of its limited sample size, we believe the Core Study may not fully address concerns about device rupture. Therefore, we recommend that you provide additional clinical information on your device (e.g., from other U.S. and/or European retrospective or prospective studies), as well as relevant information from the published literature, for the following:

- the frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel for all patients with ruptured devices (both symptomatic and asymptomatic (silent rupture) patients)

- a detailed description of the local health consequences for all patients with ruptured devices (both symptomatic and asymptomatic (silent rupture) patients), including the severity of the local health consequences and the clinical course of these patients

- the incidence, prevalence, and timing of silent ruptures that progress to symptomatic ruptures

- the incidence, prevalence, and timing of intracapsular ruptures that progress to extracapsular ruptures.

Alternative Breast Implants

Depending on the design of your alternative breast implant, FDA may recommend similar supplemental clinical information as described above for silicone gel-filled breast implants.

9.6 Supplemental Literature Information

Because of the limited sample size of the Core Study, we recommend that you provide a current review of the literature for the topics below. As stated in Section 11.4, this information should be included in the physician and patient labeling. The topics include:

- cancer and benign breast disease
- CTDs, including fibromyalgia
- interference of device with mammographic detection of tumors or rupture
- neurological disease
- ability to lactate
- offspring issues (safety of milk for breastfeeding and 2nd generation effects)
- potential systemic health consequences of extracapsular gel rupture
- suicide risk.

We recommend that you provide a thorough search of current medical literature (beginning with the 1999 IOM Report) on breast implants to address the range of clinical experience with each of the topics bulleted above as they relate to the specific type of device (i.e., silicone gel-filled, saline-filled, or alternative), as well as the criteria and method for selecting the literature. We recommend that you provide copies of the literature references and develop a table that summarizes the information.

We recommend that you provide literature information specific to the subject breast implant type. However, if no device type-specific information is available, you should provide pooled data (e.g., silicone gel and saline data) from the literature.

For alternative breast implants for which the alternative material is used in another type of medical device, we recommend that you provide a summary of the literature involving clinical experience with that material.

9.7 Postapproval Requirements

As a condition of approval of your PMA, or in connection with the approval, FDA may require you to conduct postapproval studies or to comply with restrictions relating to the sale, distribution, or use of your device. FDCA §§ 515(d)(1)(B)(ii), 519(e), 520(e), & 522 (21 U.S.C.

§§ 360e(d)(1)(B)(ii), 360i(e), 360j(e), & 360l), 21 CFR Part 814, Subpart E.) These requirements could include:

- continued follow-up of your Core Study patients based on type of device, extent of PMA data, etc. (see below for recommendations)
- additional studies to address modes and causes of rupture
- an education and certification program to train physicians and surgeons with regard to proper surgical technique, patient selection, patient monitoring, and management of complications in order to obtain access to your device
- a patient registry
- focus group study to improve the patient labeling
- other conditions, depending on the data submitted in your PMA.

For example, for a saline-filled breast implant postapproval study of Core Study patients, it may be sufficient to utilize annual mail-in questionnaires to collect information on pain, capsular contracture, deflation/rupture, reasons for reoperations, reasons for removals, and satisfaction.

For a silicone gel-filled breast implant postapproval study of Core Study patients, annual physician follow-up may be appropriate, if the risk of silent rupture for these devices, as well as other observations, require physician assessment.

For an alternative breast implant postapproval study of Core Study patients, FDA will work with you to determine the appropriate design at the time of PMA approval.

10. Clinical Data Presentation

10.1 General Information

This section describes the types of safety and effectiveness data presentations that we recommend you provide regarding your Core Study in a breast implant PMA. We encourage you to provide your own data presentations as well as those described below. While most of these presentations apply to all types of breast implants, some data presentations, such as silent rupture information, are not applicable to saline-filled breast implants.

The majority of the data described below should be reported for the **separate patient cohorts of primary augmentation, primary reconstruction, and revision** (i.e., the patient status/indication at study *entry*). See Section 9.1 above regarding specific patient cohort classification. Furthermore, you should provide the data on both per patient and per device bases for most of the items below.

10.2 Patient Accounting Presentation

We recommend that you provide the following patient accounting:

- a complete patient accounting table on a per patient basis for each separate patient cohort (see below for more details)
- the causes for patients lost to follow-up, as well as any measures to minimize such future events
- the causes for patient and physician-initiated discontinuations
- the causes of any deaths, including reports from post-mortem examinations.

Table 1 below is an example of cumulative patient accounting. You should report the deaths and removals cumulatively (i.e., continue adding across the timepoints instead of just reporting the number specific to one timepoint). You should include the following information in the patient accounting table:

Table 1 - Cumulative Patient Accounting

	Periop	1 yr	2 yr	n yr, etc
Theoretically due[A]	100	85	50	
Deaths	0	1	1	
Patients with all devices removed without replacement	0	2	2	
Patients with all devices removed and replaced with other manufacturer's devices	0	1	3	
Patients with all devices removed and replaced with your devices	0	4	6	
Expected[B]	100	81	44	
Actual (Patients with complete follow-up)	100	68	39	
Lost-to-follow-up	0	13	5	
Percent Follow-up (Actual/Expected)	100/100 (100%)	68/81 (84%)	39/44 (89%)	

[A]Patients who would have been examined according to date of implantation and follow-up schedules.

[B]Patients who are theoretically due minus the sum of the deaths, removals without replacement, and removals with replacement with different manufacturer's devices.

To allow FDA evaluation of the safety and effectiveness data, we recommend that at least 80% follow-up at each timepoint be provided.

10.3 Demographics and Baseline Characteristics

We recommend that, for each separate patient cohort, you provide the information below regarding patient demographics, as well as patient, device, and surgical baseline characteristics.

Patient Demographics (per patient basis)

- ?? patient age, height, and weight

Patient Baseline Characteristics (per patient basis)

- ?? indication for use (i.e., augmentation, reconstruction, or revision)

Device Baseline Characteristics (per device basis)

- ?? device surface type (e.g., smooth , textured)
- ?? device type (i.e., single or multi-lumen), if applicable
- ?? device style and/or size, if clinically relevant
- ?? valve type (e.g., leaf, diaphragm), if applicable

Surgical Baseline Characteristics (per device basis)

- ?? surgical incision site (e.g., periareolar, inframammary fold, axillary)
- ?? incision size
- ?? device placement (e.g., retromuscular, subglandular)
- ?? timing of reconstruction (i.e., immediate or delayed)

- use and type of surgical pocket irrigation
- use and type of intraluminal agents, if applicable.

10.4 Safety Data Presentation - Complications

Overall Sum of Complications

We recommend that you provide the overall sum of all complications on both per patient and per device bases for each separate patient cohort at each timepoint. You should provide the total number of events categorized as mild, moderate, severe, etc. (if available). If the same event occurred more than once in the same patient or breast, you should count it more than once.

Cumulative Incidence of Complications

We recommend that you provide the cumulative incidence of individual complications at each timepoint on both per patient and per device bases for each separate patient cohort. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients or devices at that timepoint.

If the same complication is reported in the same patient or breast more than once, it should be counted once in the numerator if that same complication never resolved during the entire follow-up period. If a complication occurs in a patient or breast, resolves, and then recurs at a subsequent timepoint in the same patient or breast, it should be counted twice in the numerator.

If more than one different or new complication occurs in the same patient/breast cumulatively, it should be counted more than once in the numerator and once in the denominator for per patient and per device reporting for the total (overall) data presentation.

Note that each capsular contracture grade should be considered a new or different complication and that a new (after implantation) diagnosis of breast cancer should be considered a new complication.

Kaplan-Meier Analyses of Complications

We recommend that you provide Kaplan-Meier analyses (i.e., 1 minus the complication-free survival rate over time) on both per patient and per device bases for each separate patient cohort for every complication including, but not necessarily limited to, the following:

- removal for any reason regardless of whether the device was replaced
- removal for any reason with replacement with your device
- removal for any reason with replacement with another manufacturer's device
- removal for any reason without replacement
- any reoperation
- capsular contracture grades II, III, and IV separately
- capsular contracture grades III and IV together

- capsular contracture grades II, III, and IV together
- rupture/deflation (see Section 10.5 below for more details)

Refer to ***Complications*** in Section 9.3 for additional information. Kaplan-Meier analyses should be performed for all complications, whether or not the complications may be related to the device.

To avoid the problem of competing risks, a patient who experiences one complication should still be considered a candidate to experience any other potential complication.

Reasons for Device Removal

We recommend that you provide the cumulative reasons for device removal for each separate patient cohort at each timepoint. The denominator should be the total number of devices removed since the initial implantation until that timepoint. If more than one reason for removal is reported for a given device, we recommend that you determine the primary reason for removal based on a hierarchy, such as:

- rupture/deflation
- infection
- capsular contracture
- necrosis/extrusion
- hematoma/seroma
- wrinkling
- device malposition
- asymmetry
- breast pain
- scarring
- patient request for style/size change.

Reasons for Reoperation

We recommend that you provide the cumulative reasons for reoperation for each separate patient cohort at each timepoint. The denominator should be the total number of reoperations since the initial implantation until that timepoint. If more than one reason for the reoperation is reported, you should report all reasons.

Types of Additional Surgical Procedures

We recommend that you provide the cumulative types of additional surgical procedures for each separate patient cohort at each timepoint. The denominator should be the total number of additional surgical procedures since the initial implantation until that timepoint. If more than one type of procedure is reported, you should report all procedures performed.

Kaplan-Meier Analyses of Complications Occurring After Device Removal With Replacement

We recommend that you provide the Kaplan-Meier analyses (i.e., 1 minus the complication-free survival rate over time) on a per device basis for each separate patient cohort for every complication occurring after device removal with replacement. You should use the date of device replacement as the beginning timepoint for this analysis.

10.5 Safety Data Presentation – Rupture

With regard to rupture, we recommend that you provide the incidence, prevalence, and Kaplan-Meier rates for each of the following rupture events:

- MRI diagnosis of definitive or indeterminate rupture (refer to Section 9.3), regardless of confirmation with removal. If there is disagreement between the MRI readings of the qualified MRI assessor and the local radiologist, then the worst case reading from either should be utilized in the silent rupture rate
- rupture noted at removal, regardless of MRI diagnosis
- rupture noted during the retrieval study, if performed and applicable
- overall rupture rate: rupture from any of the sources from the 3 bullets above.

For each device suspected of rupture or reported as ruptured, we recommend that you provide a summary synopsis of the dates and results of all diagnostic procedures performed related to rupture. We also recommend that you provide the actual reports of these diagnostic procedures (e.g., MRI reports, mammogram reports), as well as the surgical explant reports for devices undergoing removal with or without replacement. In addition, we recommend that you provide the final determination of each device suspected of rupture or where rupture is confirmed.

In addition, we recommend that you provide the following information for patients who have ruptured devices:

- the frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel for all patients with ruptured devices (both symptomatic and asymptomatic (silent rupture) patients)

- tissue sampling data of the surrounding breast tissue and capsule, for all patients with ruptured devices undergoing explantation, to confirm whether device constituents are present

- a detailed description of the local health consequences for all patients with ruptured devices (both symptomatic and asymptomatic (silent rupture) patients), including the severity of the local health consequences and the clinical course of these patients.

10.6 Safety Data Presentation - CTDs

CTD Diagnoses

CTD diagnoses include those listed as "rheumatic diseases" or "rheumatic syndromes" in Section 9.3 of this guidance document. We recommend that you provide the following on a per patient basis for each separate patient cohort:

- Kaplan-Meier analyses (e.g., 1 minus the Systemic Lupus Erythematosus-free survival rate over time) for each CTD diagnosis separately and for having one or more CTD diagnosis

- the cumulative incidence of CTD diagnoses at each timepoint for each CTD diagnosis separately and for having one or more CTD diagnosis. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients at that timepoint.

CTD Signs/Symptoms Categories

A symptom category is an anatomical or body function area (e.g., skin, muscle, joint, neurological, general). For example:

- skin includes alopecia, facial rash, pruritis, and echymoses
- muscle includes myalgias, muscle weakness, and elevated CRP
- joint includes arthralgia, arthritis, and morning stiffness
- neurological includes cognitive dysfunction, memory problems, and multiple sclerosis-like symptoms
- general includes fatigue, generalized pain, and fever.

We recommend that you provide the following data on a per patient basis for each separate patient cohort:

- Kaplan-Meier analysis for each symptom category

- Kaplan-Meier analysis describing patients who are free from one or more positive symptoms

- the cumulative incidence of at least one symptom per symptom category at each timepoint for each symptom category separately and for having one or more positive symptoms. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients at that timepoint.

CTD Signs/Symptoms

For each rheumatic sign/symptom or other reported sign/symptom described in Section 9.3, we recommend that you provide the following data on a per patient basis for each separate patient cohort:

- the non-cumulative point prevalence of CTD signs/symptoms at each timepoint for each CTD sign/symptom separately and for having one or more positive CTD sign/symptom

- the cumulative incidence of CTD signs/symptoms at each timepoint for each CTD sign/symptom separately and for having one or more CTD sign/symptom. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients at that timepoint.
- the status of device rupture (both MRI/asymptomatic and symptomatic), reported complications, and patient satisfaction for patients reporting CTD signs/symptoms that were not present before breast implantation

- a comparison of the incidence and types of new CTD signs/symptoms reported with information from the published literature or other comparable sources (e.g., data from patients with other types of devices, data from patients seeking other types of cosmetic surgery).

10.7 Safety Data Presentation - Mammography Data

For patients who undergo screening mammography during the study, we recommend that you provide separate analyses for each of the following events:

- mammographic suspicion for tumor regardless of biopsy results
- mammographic suspicion for tumor with a biopsy positive for malignant tumor
- mammographic suspicion for tumor with a biopsy negative for malignant tumor.

The analyses for each event should include:

- the non-cumulative point prevalence at each timepoint on both per patient and per device bases for each separate patient cohort. You should provide the numerator and denominator used and describe how these values were obtained. The denominator

should be the number of patients or devices at that timepoint.

?? the cumulative incidence at each timepoint on both per patient and per device bases for each separate patient cohort. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients or devices at that timepoint.

?? a comparison of the data obtained in the non-cumulative point prevalence and the cumulative incidence analyses with that reported in the literature for aged-matched cohorts.

10.8 Effectiveness Data Presentation

Anatomical Effect

We recommend that you provide the frequency distribution of bra cup size at baseline, end of study, and change from baseline. You should report these results on both per patient and per device bases for each separate patient cohort.

You should provide mean, median, and mode (? standard deviation) chest circumferences at baseline and at the end of the study, as well as the change. You should report these results on a per patient basis for each separate patient cohort.

For the augmentation cohort, you should provide a matched two-way table of the number of patients in each cell demonstrating a change in bra cup size from before to after implantation. The table should include the before-values on the columns and the after-values on the rows.

HRQL

We recommend that you provide the mean (? standard deviation) change in each validated measure (preoperative to each visit). You should report these results on a per patient basis for each separate patient cohort. The denominator should be the number of patients at each visit. FDA also recommends that you compare your results to published normative data for SF-36.

Patient Satisfaction

For those patients reporting dissatisfaction following breast implantation, we recommend that you provide the following information:

- stated reason for dissatisfaction
- presence, severity, status (i.e., resolved or not resolved), and method of resolution of any complications
- reports of CTD diagnoses, signs, and/or symptoms.

10.9 Pooling Analyses

We recommend that you provide data demonstrating that the patients in the study are representative of the population for whom the device is intended by providing the statistical rationale for pooling across:

- investigational site
- demographic and baseline characteristics described in Section 10.3 above.

10.10 Additional Analyses

Logistic Regression Analyses of Each Safety and Effectiveness Outcome

To determine which variables are associated with each safety and effectiveness outcome, we recommend that you provide logistic regression analyses, where appropriate, on a per device basis for each separate patient cohort using, but not necessarily limited to, the following static covariates:

- patient age
- indication for use (i.e., augmentation, reconstruction, or revision)
- device surface type (e.g., smooth, textured)
- device type (i.e., single or multi-lumen), if applicable
- device style and/or size, if clinically relevant
- valve type (e.g., leaf, diaphragm), if applicable
- surgical incision site (e.g., periareolar, inframammary fold, axillary)
- incision size
- device placement (e.g., retromuscular, subglandular)
- timing of reconstruction (i.e., immediate or delayed)
- use and type of surgical pocket irrigation
- use and type of intraluminal agents, if applicable.

Cox Proportional Hazards Regression Analyses of Rupture/Deflation

To determine which variables are associated with rupture/deflation, we recommend that you provide Cox regression analyses of rupture/deflation on a per patient basis for each separate patient cohort using the static covariates above, as well as time-dependent covariates (e.g.,

infection, capsular contracture). The coefficient estimates should be the relative risks (hazard ratios) of rupture/deflation based on transition to a complication. An advantage of this approach is that rupture/deflation is clearly defined and multiple complications can be easily handled as separate time-dependent covariates for each type of event. This also addresses the problem of competing risks.

11. Labeling

11.1 General Information

General labeling requirements for medical devices are described in 21 CFR Part 801. Additional sources of labeling requirements for IDE submissions are 21 CFR §§ 812.5 and 812.20(b)(10). An additional source of labeling requirements for PMA submissions is 21 CFR § 814.20(b)(10). Both the IDE and PMA regulations require that you provide copies of all labeling for your device(s). Additional labeling recommendations may be obtained from the guidance document, "**Device Labeling Guidance #G91-1,**" http://www.fda.gov/cdrh/g91-1.html.

Although the labeling for an IDE submission may differ from that for a PMA submission, we recommend that you provide the following labeling for your device:

- package labels
- physician labeling (i.e., package insert)
- patient labeling
- patient device card.

11.2 Package Labels

We recommend that you provide copies of all labels used in the packaging of your device. You should also include a description of where each label is attached or included in the packaged device.

The outer package label(s) should include, at minimum, the following information:

- device name, style, etc.
- device serial/lot number
- name and address of manufacturer, packer, or distributor
- quantity
- material
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- expiration date.

If the breast implant is being studied under an IDE study, then the package label(s) must include the following statement, "CAUTION - Investigational Device. Limited by Federal (or United States)

law to investigational use." (21 CFR § 812.5)

11.3 Physician Labeling

The physician labeling (i.e., package insert) for a breast implant typically involves a combination package insert/surgical technique manual. However, you may choose to provide this information in separate pieces of labeling. As a collective piece of labeling, we recommend that you provide PMA physician labeling with the following types of information:

- device name, style, etc.
- name and address of manufacturer, packer, or distributor
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- expiration date
- brief device description with material information
- indications for use
- any relevant contraindications (including surgical procedures which are contraindicated due to interference with device integrity and/or performance)
- any relevant warnings, including, but not necessarily limited to:
  - a warning against closed capsulotomy because it has been shown to potentially result in device rupture
  - a warning against the addition of substances into the filler (i.e., betadine, steroids, and antibiotics) other than those recommended because the substance may potentiate and/or accelerate delamination of the shell
- any relevant precautions
- list of potential complications[6]
- preoperative patient procedures (e.g., prophylactic antibiotics), operating room procedures (e.g., what supplies should be on hand), and troubleshooting procedures
- instructions for implantation, including surgical approach and device specific information (depends on type of breast implant)
- intraoperative test procedures to ensure device integrity and proper placement (if necessary)
- instructions for follow-up, including whether patient antibiotic prophylaxis is recommended during the post-implant period or during any subsequent surgical

[6] We recommend that you refer to the FDA breast implant consumer handbook entitled, "**Breast Implants – An Information Update**" for additional information regarding potential complications. This handbook is available through FDA's breast implant website at http://www.fda.gov/cdrh/breastimplants/.

procedures, postoperative patient care, etc.

- instructions for monitoring device integrity and placement
- appropriate clinical study safety and effectiveness results
- appropriate preclinical study results, including gel bleed results
- updated information from the literature as per Section 9.6 above
- recommendations for method(s) and frequency of screening for rupture
- clinical management of suspicious and confirmed rupture.

The IDE physician labeling should include all elements identified in the bullets above except for those involving specific clinical data results. In addition, the IDE physician labeling must include the following statement, "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use." (21 CFR § 812.5).

You should make the physician labeling available to the patient prior to the surgery, upon request, whether the request comes directly from the patient or through the physician/surgeon.

11.4 Patient Labeling

The purpose of the patient labeling is to provide a patient with sufficient information (e.g., realistic expectations of the benefits and risks) so that she may make an informed decision as to whether or not to receive breast implants. Currently, for PMA-approved breast implants, patient labeling is generically referred to as a patient brochure, a patient booklet, or patient informed decision labeling. We recommend that you include patient labeling in your PMA submission, and that it include the following types of information:

- device names, styles, etc.
- brief device description with material information
- indications for use
- relevant contraindications, warnings, and precautions
- potential complications, including the possible methods of resolution
- anticipated benefits
- surgical alternatives, including no treatment or no implants and the benefits and risks of each
- postoperative care, including what to expect after surgery, symptoms to tell doctor about immediately, length of recovery, physical limitations, etc.
- factors to consider in deciding whether or not to get breast implants (e.g., may not be lifetime device or one-time surgery, many of the changes to breasts following implantation are irreversible, breast implants may affect the ability to breast feed, routine screening mammography may be more difficult, health insurance coverage issues)

- other factors to consider (e.g., choosing a surgeon, device size and shape, surface texturing, palpability, device placement, incision sites)
- additional information related to the device such as lifetime replacement and reimbursement policy information, including estimated cost for replacement, costs not covered, etc.
- instructions for patients on how to monitor their breast implants
- toll-free number for questions/information
- appropriate clinical study safety and effectiveness results
- appropriate preclinical study results, including gel bleed results
- updated information from the literature as per Section 9.6 above
- recommendations for method(s) and frequency of screening for rupture
- clinical management of suspicious and confirmed rupture.

We recommend that you encourage physicians/surgeons who use your device to provide the patient labeling to the patient at the initial visit/consultation so that she has sufficient time to review the information and discuss any issues with her physician/surgeon as part of her decision making process.

For an IDE study, there is a required informed consent document (21 CFR Part 50). The specific elements of informed consent are described in 21 CFR § 50.25. Although an informed consent document is not patient labeling, we recommend that the informed consent document describe the purpose of the clinical study, the potential risks, and any other appropriate elements identified from the bulleted list for the PMA patient labeling above. Note that the informed consent document required for a patient to participate in an IDE study should not be confused with a standard surgical consent form that a hospital requires to be signed by any surgical patient.

PMA patient labeling and the IDE informed consent document should not exceed the reading comprehension level that is easily read and understood by most readers in the United States. You should keep technical terms to a minimum and define any that are used. For additional information, we recommend that you refer to "**Guidance on Medical Device Patient Labeling**" at http://www.fda.gov/cdrh/ohip/guidance/1128.pdf and information regarding plain language at http://www.plainlanguage.gov.

We also recommend that you refer to the FDA breast implant consumer handbook entitled, "**Breast Implants – An Information Update**" for additional information regarding potential complications, factors to consider, surgical alternatives, etc. This handbook is available through FDA's breast implant website at http://www.fda.gov/cdrh/breastimplants/.

11.5 Patient Device Card

We recommend that you provide patient device cards as part of the informed consent process for your IDE study and as part of the patient labeling for your PMA-approved device. This piece of labeling has been referred to in different ways by manufacturers, such as manufacturer device card,

patient identification card, or patient information card. Regardless of the name used, its purpose is to provide the patient with specific information about her device(s). The device card should include, but need not be limited to, the device's style, size, and serial/lot number. Typically, multiple device labels/stickers are provided with the device card that includes this information. If that is the case, at the time of surgery, one label/sticker should be placed in the patient's records and one label/sticker should be placed on the device card. We recommend that the physician/surgeon give the device card to the patient immediately following surgery.